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Original article

Anthracycline-induced acute cardiotoxicity in adults treated for leukaemia

Analysis of the clinico-pathological aspects of documented acute anthracycline-induced cardiotoxicity in patients treated for acute leukaemia at the University Hospital of Zürich, Switzerland, between 1990 and 1996

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Summary

Background: Acute cardiotoxicity due to anthracyclines is a rare, but life-threatening event. Interindividual sensitivity to anthracyclines is highly variable and cannot be predicted for the individual patient.

Patients and methods: This is a retrospective study. Medical charts and autopsy reports of patients treated for acute leukemia between 1990 and 1996 at the University Hospital of Zürich, Switzerland were reviewed and searched for anthracycline-associated acute cardiotoxicity. Patients with pre-existing heart disease known to be associated with cardiotoxicity were excluded.

Results: Seven patients treated for leukemia with proven anthracycline-associated acute cardiotoxicity were included. In six patients the direct cause of death was acute cardiotoxicity due to the treatment. One patient recovered from cardiac failure but died a few months later from refractory leukemia. Clinical symptoms were those of a heart failure. Pathological findings were dilatative cardiac hypertrophy and pericardial effusion. Microscopically the typical findings of myocardial fibrosis and perinuclear vacuolisated myocytes were seen.

Conclusions: The awareness of acute adverse effects on cardiac performance by anthracyclines faciliates early recognition and prevention of heart failure. Reliable tests are needed for the early diagnosis of subclinical myocardial damage in order to identify patients at risk.

Key words: anthracycline-associated acute cardiotoxicity, clinical symptoms, pathological findings

Introduction

Anthracyclines, most commonly daunorubicin, idarubicin or mitoxantrone are highly efficacious antineoplastic agents for acute myeloid leukemia (AML). However, their therapeutic potential is limited by the ocurrence of cardiotoxicity [1–6].

Three distinct types of anthracycline-induced cardiotoxicity have been described [7]. Chronic cardiotoxicity resulting in cardiomyopathy is well known and clinically the most important form [2, 10]. Chronic cardiomyopathy usually occures within one year of treatment [2]. The cumulative dose is a well known important risk factor. Today, late onset of anthracycline-induced cardiotoxicity causing ventricular dysfunction [11–13] and arrhythmia [14–16] is recognised more often than earlier. Its manifestations occure years or decades after a prolonged asymptomatic period.

The acute injury becomes clinically manifest during or immediately after anthracycline administration long before the assumed total cumulative toxic dose is reached. However, with the current cytotoxic drug regimens it is thought to be a relatively rare unwanted side effect. Clinicians are often not aware of the potential risk and less severe episodes are most likely missed. Acute cardiotoxicity presents mainly with transient arrhythmias or ST/T changes in ECG [8], with a pericarditis-myocarditis syndrome or acute cardiac decompensation [9].

Aim of this retrospective study is to analyse the frequency and clinico-pathological aspects of documented acute anthracycline-induced cardiotoxicity in patients treated for acute leukemia.

Patients and methods

The medical records of 165 patients treated for acute leukemia between 1990 and 1996 at the University Hospital of Zürich, Switzerland, were reviewed. All patients with known pre-existing heart disease, including coronary artery disease or risk factors for it, heart disease due to the malignancy or mediastinal radiation were excluded.

Included were patients who during or immediately after administration of combination chemotherapy with anthracycline developed clinical or radiological evidence oft left ventricular (LV) decompensation with dyspnea and pulmonary rales, cardiomegaly or signs of pulmonary hypertension on chest X-ray.

Pathologic-anatomical manifestations for anthracycline associated cardiotoxicity were hypertrophy [17, 18], cardiomegaly [17, 19], pericarditis [2, 7, 17, 20], pericardial effusion [17] and myocarditis [7]. The histological criteria were myofibrillar loss, distension of the sarcoplasmatic reticulum, and cytoplasmatic vacuolisation, diffuse cell damage (total loss of contractile elements, loss of organelles, mitochondrial and nuclear degeneration) [1].

Results

In our series, six males and one female, age 19 to 66 years (median 41) met the criteria of anthracycline-associated acute cardiotoxicity. All patients were treated with curative intention, six for a *de novo* AML (FAB classification: two patients M0, two patients M1, one patient M4, one patient M6) and one for relapsing disease.

All patients but one received conventional doses of anthracycline for treatment.

In one patient a ten-fold overdose of mitoxantrone was accidentally infused.

Clinical course and findings

Clinical symptoms were those of left (6 of 7) or biventricular heart failure (1 of 7) with dyspnea and orthopnea, tachycardia, pulmonary oedema and elevated jugular venous pressure. The first symptoms occured in three patients during the first course, in three patients during the second and in one patient after the third course of treatment. All of them recoverd from the first episode but six patiens died of cardiotoxicity during the following course with anthracycline. Only one patient recovered again.

At the time of clinical symptoms of cardiac toxicity the chest X-ray was abnormal in all seven patients. Six of seven had a cardiomegaly, two of seven signs of pulmonary venous congestion and two of seven pleural effusion. In three patients pulmonary venous congestion as well as pleural effusion were present.

An electrocardiogram was registred in six of seven patients before starting chemotherapy. In two of them (P4 and P5) an incomplete right bundle branch block was pre-existent. On treatment, a rapid atrial flutter became manifest in one patient (P1), premature ventricular complexes in another (P3). One patient (P7) developed supraventricular arrhythmia and polymorph premature ventricular complexes. In four patients (P1, P4, P6 and P7) diffuse repolarisation abnormalities appeared. In one patient an AV-block I° occurred in combination with a total right bundle branch block.

An echocardiography was done in three patients (P1, P4, and P6) after the occurrence of cardiac abnormalities: two patients (P1, P4) had a haemodynamically not relevant pericardial effusions with normal ejection fraction, one patient (P6) a decreased ejection fraction of 30%.

Treatment and outcome

Six patients (P1, P3–7) needed specific heart failure treatment with diuretics, angiotensin converting enzyme inhibitors (P4, P6) and catecholamines (P3, P5, P6). Three patients received digitalis (P1, P6, P7), and one patient (P7) lidocaine.

All seven patients died 65–450 (median 129) days after start of chemotherapy. The death of six patients was due to acute cardiotoxicity. Anthracycline-associated cardiopathy was confirmed by histo-pathological findings. One patient recovered from a clinically well documented episode of severe heart failure but died later from progressing disease. An autopsy was refused.

Table 1. Chemotherapy total dose mg/m^2.

Pt	DNR	Ida	Mito	Ara-C	VCR	m-AMSA	VP-16
1M	288			26265	0,8	618	403
2M	135		80	8700	0,75	600	400
3M	135		42,4	10544			
4M	135			25400		720	
5M		36	450[a]	21400		360	
6M	135		140	15400			1000
7F		80		1900			

Abbreviations: DNR – daunorubicin; Ida – idarubicine; Mito – mitoxantrone; Ara-C – cytosinarabinoside; VCR – vincristine; m-AMSA – amsacrine; VP16 – etoposide.
[a] Ten-fold overdose.

Table 2. Cardiac findings.

Pt	Clin. signs of congestive heart failure	Abnormal chest X-ray[a]	Abnormal ECG[a]	Abnormal echo[a]	Time of death after start of treatment
1M	Yes	Yes	Yes	Yes	69 d
2M	Yes	Yes	No	nd	129 d
3M	Yes	Yes	Yes	nd	65 d
4M	Yes	Yes	Yes	Yes	88 d
5M	Yes	Yes	Yes	nd	147 d
6M	Yes	Yes	Yes	Yes	266 d
7F	Yes	Yes	Yes	nd	450 d

Abbreviation: nd – not done.
[a] For details see text.

Table 3. Autopsy results[a] (n = 6).

Myocardial fibrosis	5
Endomyocardial fibrosis	1
Hypertrophy	6
Dilatation	3
Pericardial effusion	4
Peri-/epicarditis	1
Subendocardial haemorrhage	3
Myocardial necrosis	3

[a] For details see text.

Autopsy

Autopsy was performed in six of seven patients (P1–P5, P7). Macroscopically, the heart was hypertrophic in all six patients, dilatated in three (P4, P5, P7). In four (P1, P2, P4, P5) pericardial effusion was present. A fibrous, sterile peri-/epicarditis was seen in one (P1), epicardial bleeding in two (P3, P4), endocardial haemorrhage in one (P3) patient. Microscopically typical morphological features of acute anthracycline-induced cardiotoxicity

such as myocardial fibrosis and perinuclear vacuolisated myocytes were seen in five patients (P1, P2, P4, P5, P7). One (P3) had endomyocardial fibrosis. In three patients (P3, P4, P7) myocardial necrosis was seen: in one (P3) myocardial necrosis was subendocardial, in one (P7) diffuse and one patient (P2) had papillary muscle necrosis. All six patients had normal, wide coronary arteries. Additionally, one patient (P3) had a sterile abscess (diameter 3 mm) in the left ventricle of unknown aetiology.

Discussion

Over a period of six years, 165 patients were treated for acute leukemia at the University Hospital of Zurich, Switzerland. In seven of them, acute cardiotoxicity attributable to anthracycline-based chemotherapy was observed. This is relatively a rare complication and probably often missed. The true incidence remains unknown. Patients with probable subclinical acute cardiotoxicity are missed. In this study, patients with additional cardiac risk factors were not taken into account.

The most important risk factor for the development of chronic cardiotoxicity is the total cumulative dose. In contrast, the event of acute cardiotoxicity is not predictable and occurs unexpectedly. There seems to be a large variation in individual sensitivity. Often, clinicians are not aware of the potential risk. Less severe episodes are therefore missed. In our experience, the possibility of drug-induced cardiotoxicity was taken into consideration late in the course. One reason was that these mostly young, previously healthy patients without pre-existing heart disease are in reduced general condition which is ascribed to the life-threatening disease, the aggressive treatment and its well-known side effects. Early diagnosis could contribute to the prevention of drug-induced heart failure with fatal outcome in the acute phase, possibly also reduce the rate of chronic or late-onset anthracycline-induced cardiotoxicity.

The main problem is the lack of reliable tests for early detection of subclinical cardiac tissue damage. Clinical manifestations of heart failure, ECG changes or echocardiography are neither sensitive enough nor specific in an early stage. Radioimmunoscintigraphy is sensitive, but its specificity low. Endomyocardial biopsy examination is considered to be the most sensitive and specific method for anthracycline-induced cardiotoxicity and for prediction of cardiac dysfunction [12]. This method is invasive and restricted to medical centres. Therefore, the use for routine monitoring is limited.

There ar no reliable laboratory tests for early detection of myocardial damage. The release of cardiac troponin T (cTnT) as a biomarker of doxorubicin-induced chronic cardiac injury has been evaluated in the spontaneously hypertensive rat (SHR) model. Monitoring serum levels of cTnT can detect doxorubicin-induced myocyte damage and may prove to be useful for the non-invasive evaluation of cardiac toxicity in humans [29]. Fink et al. [30] evaluated 35 anthracycline-containing chemotherapy courses in 22 children with cancer. Within 72 hours from anthracycline therapy no increment of one of these marker proteins was detected.

Atrial natriuretic peptide (ANP), mainly from the atrium, and brain natriuretic peptide (BNP), mainly from the ventricle, provide prognostic information independent of other variables associated with a poor prognosis in patients with chronic heart failure [31]. Natriuretic peptides might be useful in the detection of subclinical left ventricular dysfunction as indication for cardiomyoathy [34, 35]. Their predictive value for clinically relevant damage is not yet known. Prospective studies have to prove their diagnostic benefit.

Strategies for prevention of anthracycline-associated cardiotoxicity have to be developed. Chelating agents like ICRF 187 (dexrazoxane) and antioxidative WR-2721 (amifostine) have been applied in combination with anthracyclines [26, 33]. Proving their efficacy is difficult again due to the lack of established tests recording already minimal cardiac damage. Early administration of the ACE inhibitor may be an other therapeutic possibility.

Acute cardiotoxicity of anthracyclines is a rare, but life-threatening event. Sensitiveness to anthracyclines is interindividually highly variable and not predictable. The awareness of potential adverse effects on cardiac performance by anthracyclines may contribute to early diagnosis and prevention of drug-induced heart failure. Reliable tests are needed for early diagnosis of subclinical myocardial damage in order to identify patients at risk.

References

1. Bristow MR, Mason JW, Billingham ME, Daniels JR. Dose effect and structure function relationships in doxorubicin cardiomyopathy. Am Heart J 1981; 102 (4): 709–18.
2. Von Hoff DD, Layard MW, Basa P et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979; 91 (5): 710–7.
3. Isner JM, Ferrans VJ, Cohen SR et al. Clinical and morphological findings after anthracycline therapy Am J Cardiol 1983; 51 (7): 1167–74.
4. Praga C, Beretta G, Vigo PL et al. Adriamycin cardiotoxicity: A survey of 1273 Patients. Cancer Treat Rep 1979; 63 (5): 827–34.
5. Billingham ME. Endomyocardial changes in anthracycline-treated patients with and without irradiation. Front Radiat Ther Oncol 1979; 13: 67–81.
6. Ettinghausen SE, Bonow RO, Palmeri ST et al. Prospective study of cardiomyopathy induced by adjuvant doxorubicin therapy in patients with soft-tissue sarcomas. Arch Surg 1986; 121 (12): 1445–51.
7. Shan K, Lincoff M, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med 1996; 125: 47–58.
8. Steinberg JS, Cohen AJ, Wasserman AG et al. Acute arrhythmogenicity of doxorubicin administration. Cancer 1987; 60 (6): 1213–8.
9. Ferrans VJ. Overview of cardiac pathology in relation to anthracycline cardiotoxicity. Cancer Treat Rep 1978; 62 (6): 955–61.
10. Bristow MR, Mason JW, Billingham ME et al. Doxorubicin cardiomyopathy: Evaluation by phonocardiography, endomyocardial biopsy and cardiac catheterisation. Ann Intern Med 1978; 88 (2): 168–75.

11. Schwartz RG, McKenzie WB, Alexander J et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Am J Med 1987; 82 (6): 1109–18.
12. Haq MM, Legha SS, Choksi J et al. Doxorubicin-induced congestive heart failure in adults. Cancer 1985, 56 (6): 1361–5.
13. Steinherz LJ, Steinherz PG, Tan CT et al Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991, 266 (12): 1672–7.
14. Yeung ST, Yoong C, Spink J et al. Functional myocardial impairment in children treated with anthracyclines for cancer. Lancet 1991; 337 (8745): 816–8.
15. Larsen RL, Jakacki RI, Vetter VL et al. Electrocardio graphic changes after cancer therapy in children and young adults. Am J Cardiol 1992; 70 (1): 73–7.
16. Lipshultz SE, Colan SD, Gelber RD et al. Late cardiac effects of doxorubicin therapy for ALL in childhood. N Engl J Med 1991; 324 (12)· 808–15.
17. Bristow MR et al. Early anthracycline cardiotoxicity. Am J Med 1978; 65: 823–32.
18. Buzdar AU, Marcus C, Smith TL, Blumenschein GR. Early and delayed clinical cardiotoxicity of doxorubicin. Cancer 1985; 55: 2761–5.
19. Lefrak EA, Pitha J, Rosenhelm S et al. A clinical pathologic analysis of adriamycin cardiotoxicity. Cancer 1973; 32: 302–14.
20. Goorin AM, Borow KM, Goldman A et al. Congestive heart failure due to adriamycin cardiotoxicity. Cancer 1981, 47 (12): 2810–6.
21. Von Hoff DD, Rozencweig M, Layard M et al. Daunomycin-induced cardiotoxicity in children and adults. Am J Med 1977; 62 (2): 200–8.
22. Pratt CB, Ransom JL, Evans WE. Age-related adriamycin cardiotoxicity in children. Cancer Treat Rep 1978; 62 (9): 1381–5.
23. Halazun JF, Wagner HR, Gaeta JF, Sinks LF. Daunorubicin cardiac toxicity in children with ALL. Cancer 1974; 33 (2): 545–54.
24. Sorensen K, Levitt G, Sebag-Montefiore D et al. Cardiac function in wilms'tumor survivors. J Clin Oncol 1995; 13 (7): 1546–56.
25. Torti FM, Bristow MR, Howes AE et al. Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule. Ann Intern Med 1983; 99 (6): 745–9.
26. Wexler LH. Ameliorating anthracycline cardiotoxicity in children with cancer: Clinical trials with dexrazoxane. Semin Oncol 1998, 25 (4 Suppl 10): 86–92
27. Dorr RT. Cytoprotective agents for anthracyclines Semin Oncol 1996; 23 (4 Suppl 8). 23–34
28. Bassand JP. Left ventricular remodelling after acute myocardial infarction-solved and unsolved issues. Eur Heart J 1995; 16 (Suppl 1): 58–63.
29. Herman EH; Lipshultz SE; Rifai N et al. Use of cardiac troponin T levels as an indicator of doxorubicin-induced cardiotoxicity. Cancer Res 1998; 58 (2): 195–7.
30. Fink FM, Genser N, Fink-C et al. Cardiac troponin T and creatine kinase MB mass concentrations in children receiving anthracycline chemotherapy. Med Pediatr Oncol 1995; 25 (3): 185–9.
31. Tsutamoto T, Wada A, Maeda K et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997; 96 (2). 509–16.
32. Weber KT, Sun Y, Campbell SE. Structural remodelling of the heart by fibrous tissue: Role of circulating hormones and locally produced peptides. Eur Heart J 1995; 16 (Suppl N): 12–8.
33. Singal PK; Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med 1998; 339 (13): 900–5.
34. Nousiainen T, Jantunen E, Vanninen E et al. Natriuretic peptides as markers of cardiotoxicity during doxorubicin treatment for non-Hodgkin's lymphoma. Eur J Haematol 1999; 62 (2): 135–41.
35. Nousiainen T, Jantunen E, Vanninen E et al. Acute neurohumoral and cardiovascular effects of idarubicin in leukemia patients. Eur J Haematol 1998; 61 (5): 347–53.
36. Green DM, Hyland A, Chung CS et al. Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence JCO 1999; 3207–3215.
37. Seifert CF, Nesser ME, Thompson DF. Dexrazoxane in the prevention of doxorubicin-induced cardiotoxicity. Ann Pharmacother 1994; 28 (9): 1063–72.

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